Universität Zürich

Zentrum für Zahnmedizin
Vorsteher: Prof. Dr. med. dent. Ch. Hämmerle

Klinik für Kieferorthopädie und Kinderzahnmedizin
Direktor: Prof. Th. Eliades, DDS, MS, Dr Med Sci, PhD

Arbeit unter Leitung von Dres. med. dent. M. Hänggi und R. Patcas

Pharyngeal airway dimensions and their physiological changes based on lateral cephalometric radiographs in healthy children aged 6 to 17

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Barbara Maria Mislik
von Österreich

Genehmigt auf Antrag von Prof. Th. Eliades, DDS, MS, Dr Med Sci, PhD

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I would like to dedicate my thesis to my beloved parents

Hinweis auf geplante Publikation

Eine verkürzte Version der vorliegenden Dissertationsarbeit wurde für eine Publikation mit der Dissertantin als Erstautorin eingereicht.

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1. Abstract

Aim: To assess the pharyngeal airway dimensions and their physiological changes based on lateral cephalometric radiographs from healthy untreated children between 6 and 17 years of age.

Material and Methods: The sample consisted of 880 lateral cephalograms (412 females and 468 males) of the Zurich craniofacial Growth study performed in the years of 1981-1984. Only healthy children 6 to 17 years of age of Caucasian ethnicity with no history of orthodontic treatment were included in the original growth study. Two anterior-posterior cephalometric airway dimensions were defined: Distance "p" as the shortest distance between the soft palate and the posterior pharyngeal wall, and distance "t" as the shortest distance between the tongue and the posterior pharyngeal wall. Statistical analyses on cephalometric measurements of airway dimensions and craniofacial parameters were performed. To disclose the age-related differences of distances "p" or "t", a one-way ANOVA together with the Sheffé post-hoc-test were applied. The influence of gender on distances "p" and "t" was analysed by a Mann-Whitney-U-test for each age group separately. The Spearman correlation was computed in order to investigate associations between clinical parameters in the data set. Variables associated with distances "p" or "t" were chosen for multiple regression model investigation.

Results: The results demonstrated high interindividual variations. A slight influence of age on distance "p" (p=0.046) could be attested (+1.03mm), but no influence on distance "t" (p=0.138). The latter decreased to some extent between 6 and 12 years of age, after that increased slightly up to age 17. No significant differences between the genders were reported for both distances

“p” and “t”, with one exception: within the 9-years-age-group, significant differences between the genders were found for “t” (p=0.009) and “p” (p=0.002). Correlation analysis demonstrated several statistically significant correlations between distance “t“ or distance “p“ and cephalometric parameters. Distance “t” revealed to be associated to ratio B/N, ratio A+B/N, SNA, SNB and a significant negative correlation with NS/Gn was found. For distance “p“, positive correlations existed with ratio B/N, ratio A+B/N, SNA, SNB and negative correlations with NS/Gn and SpaSpp/MGo. All correlation coefficients were, however, very low. A regression model was developed based on correlating variables, but the adjusted coefficient of determination revealed the regression model to be very weak.

Conclusion: Distances “p” and “t” show high interindividual variations. This renders the use of a mean value as reference value on individuals questionable. A marginal, yet continuous increase between 6 and 17 years of age was observed for distance “p”, but not for “t”. No differences between genders could be established, and only weak correlations of distance “p” and “t” to the cephalometric landmarks were found. The results indicate that upper airway dimensions in growing children from 6 to 17 years of age remain remarkably stable on average and suggest that the airway dimensions are being established in early childhood.

2. Introduction

Interest in upper airway shape and dimensions has increased steadily during the past few decades, mainly due to the appreciation of the relationship between upper airway configuration and obstructive sleep apnea (OSA) as well as its relation to craniofacial morphology in general (Guijarro-Martinez and Swennen, 2011).

Changes in normal airway function may contribute to medical disorders related to breathing, such as OSA. In adults, OSA is a common and frequently undiagnosed medical disorder (Young *et al.*, 2002) and is characterized by recurrent pharyngeal airway obstruction during sleep. Breathing disorders, similar to OSA described in adults, have also been reported in children and adolescents (Guilleminault *et al.*, 1976). Common to all cases and ages, the upper airway obstruction most often results from a combination of anatomic factors that predispose the airway to collapse during inspiration, combined with an insufficient neuromuscular compensation during sleep to maintain airway patency (Young *et al.*, 2002).

Concerning the physical principles of airflow during respiration, two important laws should be noted. Firstly, the Hagen-Poisseuilles law states that the resistance in a tube is inversely proportional to the fourth power of the radius. Thus, halving the size of the tube will increase the resistance by 16 times. Equally important for airway patency is Bernoulli's principle, which describes that the intraluminal pressure decreases as the airflow velocity increases. This second law will have important ramifications in the upper airway, which is not a rigid tube that would easily withstand negative intraluminal pressure, but is rather a flexible and collapsible structure owing to its anatomical lack of bony or cartilaginous support. Therefore the patency of the upper airway depends on a fine balance between the negative intrapharyngeal pressure developed during inspiration and its counteraction by dilating muscles (Friberg, 1999)

Children possess large adenoids and tonsils. This influences the pattern of breathing through increase of airway resistance. It is therefore not uncommon to identify children with a breathing pattern characterized by mouth breathing and an "adenoid face" (Peltomaki, 2007). Compared to faces of healthy children, such children with oral breathing pattern will have several specific features including incompetent lip seal, a narrow upper dental arch, retroclined mandibular incisors, increased anterior face height, a steep mandibular plane angle and a retrognathic chin (Linder-Aronson, 1970).

Frequent episodes of hypoxia and awakenings disrupt continuous sleep and even mild OSA is associated with significant morbidity (Young *et al.*, 2002). The sleep reduction has been reported to give rise to hypertension, cardiac arrhythmias, nocturnal angina and myocardial ischemia (Klitzman and Miller, 1994). Particularly children may present excessive daytime sleepiness, decrease in school performance, abnormal behavior, enuresis, morning headache, weight disturbances and the progressive development of hypertension. These symptoms and signs should suggest the possibility of a OSA syndrome when associated with loud snoring interrupted by pauses during sleep (Guilleminault *et al.*, 1976).

Early diagnosis of OSA is imperative in order to promote normal facial development (Aboudara *et al.*, 2009). Small pharyngeal dimensions established early in life may predispose to later OSA and snoring, when subsequent soft tissue changes caused by normal ageing, obesity or genetic background further reduce the patency of the oropharynx (Martin *et al.*, 1997). In fact, deficiency or alteration of normal airway function during the active facial growth period may have a profound influence on facial development, and diagnosing OSA by the time a patient appears to the first orthodontic evaluation and treatment might already be too late.

First and foremost sign of OSA are pathologic breathing and sleeping pattern, which may be evaluated and recorded in the patient's history. Lateral cephalograms have, to no little extend, also been used to diagnose restricted dimensions of the oropharynx.

The reproducibility of airway dimensions on lateral cephalograms has been studied extensively in orthodontic literature and is found to be highly accurate in natural head position (Malkoc *et al.*, 2005). Morphometric measurement in lateral cephalograms is an established approach to investigate the airway in OSA subjects and has been widely employed for diagnostic purposes (Battagel *et al.*, 2000; Kuhnel *et al.*, 2005).

Several investigators have also used lateral cephalometric radiographs in an attempt to identify morphological parameters that might be characteristic of OSA subjects (Battagel and L'Estrange, 1996).

Further airway studies have found minimal airway dimensions, measured on lateral cephalometric radiographs in healthy children, to be around 10-12 mm at its shortest distance between the tongue and the posterior pharyngeal wall and 9-10mm at its shortest distance between the soft palate and the posterior pharyngeal wall. (de Freitas *et al.*, 2006; Hanggi *et al.*, 2008; Pirila-Parkkinen *et al.*, 2011; Bollhalder *et al.*, 2012). Little is known about the development of airway dimensions in healthy children. McNamara found no noticeable changes with age and expressed the average value of the pharyngeal airway measurements to be between 10 and 12mm (9 – 11 mm without magnification) (McNamara, 1984).

The aim of this retrospective cross-sectional study was to evaluate the pharyngeal airway dimensions and their physiological changes based on a large sample size of lateral cephalometric radiographs from healthy untreated children aged between 6 and 17 years of age. To our knowledge, no previous attempt has been made so far to study airway dimensions on such a large sample size, enabling to classify all measurements according to age and gender.

3. Material and Methods

Subjects

The lateral cephalograms used for this study were derived from the Zurich Craniofacial Growth Study performed in the years 1981-84 at the Department of Orthodontics and Paediatric Dentistry of the University of Zurich. In the original study, 884 healthy schoolchildren of Caucasian ethnicity from local public schools with no history of orthodontic treatment were selected and examined randomly. The examination always took place very close to the individual's birthday, and 488 subjects had a second examination exactly a year later. Legal approval for releasing the data was obtained by the Federal Commission of Experts for Professional Secrecy in Medical Research (see chapter 8).

As the majority of the subjects only had one radiograph performed, a longitudinal examination could not be carried out. In the few cases where more than one radiograph existed, only the first radiograph was selected, in order to ensure a purely cross-sectional study. All cephalograms utilized for this study had to be of good quality and the airway had to be clearly visible. Thus, the final sample used consisted of 880 cephalograms. 412 subjects were female, 468 were male.

Methods

All cephalograms were taken with the same custom-made x-ray device (COMET, 3175 Flamatt, Switzerland) in a standardized position: The teeth were in centric occlusion, the head was aligned with the Frankfort horizontal plane parallel to the floor. This position was stabilized with ear rods and a nasal support to prevent the head from rotating during exposure. The focuscoronal plane distance was 200cm, film-coronal plane distance was 15cm and the magnification was 7.5%.

All radiographs were hand-traced using a 0.3mm lead on a 0.10mm matte acetate tracing paper. Three investigators who had been calibrated previously by a board-certified orthodontist, traced and landmarked the lateral cephalograms by hand according to the definitions listed in Table 1 and shown in Figures 1A and B. The digitizing was performed using a tablet digitizer (NumonicsAccuGrid, Lansdale, Pennsylvania, USA) with a resolution of 1milli-Inch. The digitized cephalometric values were calculated using self-written software.

For the assessment of the dimension of the airway, two distances were defined and evaluated: distance "p", as the shortest distance between the soft palate and the posterior pharyngeal wall, and distance "t" as the shortest distance between the tongue and the posterior pharyngeal wall.

In addition to the conventional measurements of SNA- and SNB-angle for pro- and retrognathism, distance ratios were also introduced. Three distances parallel to the Frankfort horizontal plane, perpendicular to a vertical line through point Sella, were measured to point Nasion, point A and point B, respectively (Figure 1B). Subsequently, three ratios were defined as: distance to point A / distance to point N ("ratio A/N"), distance to point B / distance to point N ("ratio B/N"), distance to point (A+B) 0.5 / distance to point N ("ratio AB/N").

38 cephalograms were traced a second time more than 6 months apart, 19 by the same investigator and 19 by a different investigator, in order to determine intra- and interobserver reproducibility.

Table 1 *Definition of the skeletal and dental landmarks in the lateral cephalometric analysis used in this study.*

Sella (S)	Centre of the Sella turcica. (Higley 1954)
Nasion (N)	Most anterior point of the Sutura nasofrontalis. (Downs 1948)
Spina nasalis anterior (Spa)	Most anterior point of the anterior nasal spine. (Sassouni 1971)
Spina nasalis posterior (Spp)	Projection of the most caudal point of the Fossa pterygopalatina onto the nasal floor. (Sassouni & Setareanos 1974)
Point A (A)	The deepest midline point on the premaxilla between the anterior nasal spine and prosthion. (Downs 1948)
Point B (B)	The deepest midline point on the mandible between infradentale und pogonion. (Downs 1948)
Menton (M)	Lowest point of the radiologic profile on chin. (Jacobsen & Caufield 1985)
Gonion (Go)	Intersection of the angle bisector of the two mandibulary tangents through Articulare and Menton with the latero-basal contour of the mandible. (Jacobsen & Caufield 1985)
Orbitale (Or)	Lowest point of the infraorbital margin. (Björk 1947)
Porion (Po)	Highest point on the upper margin of the porus acusticus externus. (Ricketts 1960)
Articulare (Ar)	Point of Intersection of the dorsal contours of process articularis mandibulae and os temporale. (Björk 1947)
Basion (Ba)	Most caudal point of the Clivus.
Pogonion (Pg)	Most prominent point of the chin / on the symphysis of the mandible. (Jacobsen & Caufiel 1985)
Menton (M)	Lowest point of the contour of the mandibular symphysis. (Jacobsen & Caufield 1985)
Distance "p"	The shortest distance between the soft palate and the posterior pharyngeal wall.
Distance "t"	The shortest distance between the tongue and the posterior pharyngeal wall.

Figure 1A*. Cephalometric points and pharyngeal distances used in this study. Distance "p" was defined as the shortest airway distance between the soft palate and the posterior pharyngeal wall and distance "t" was defined as the shortest distance between the tongue and the posterior pharyngeal wall.*

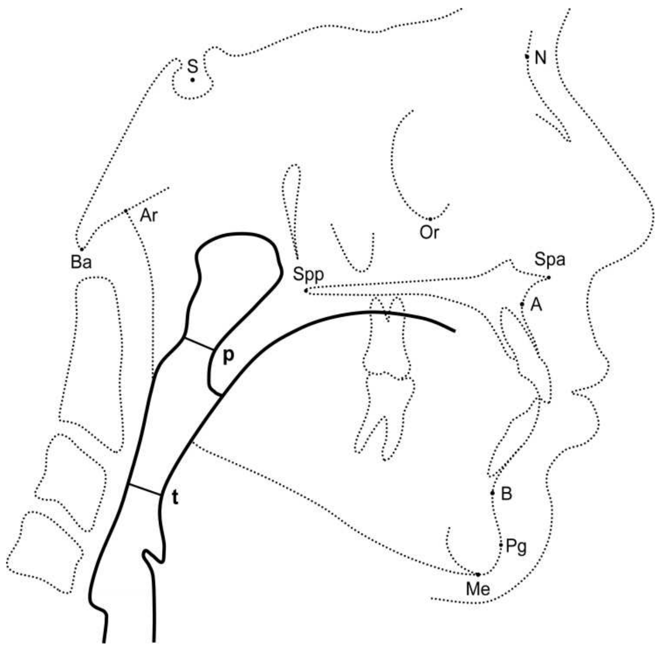
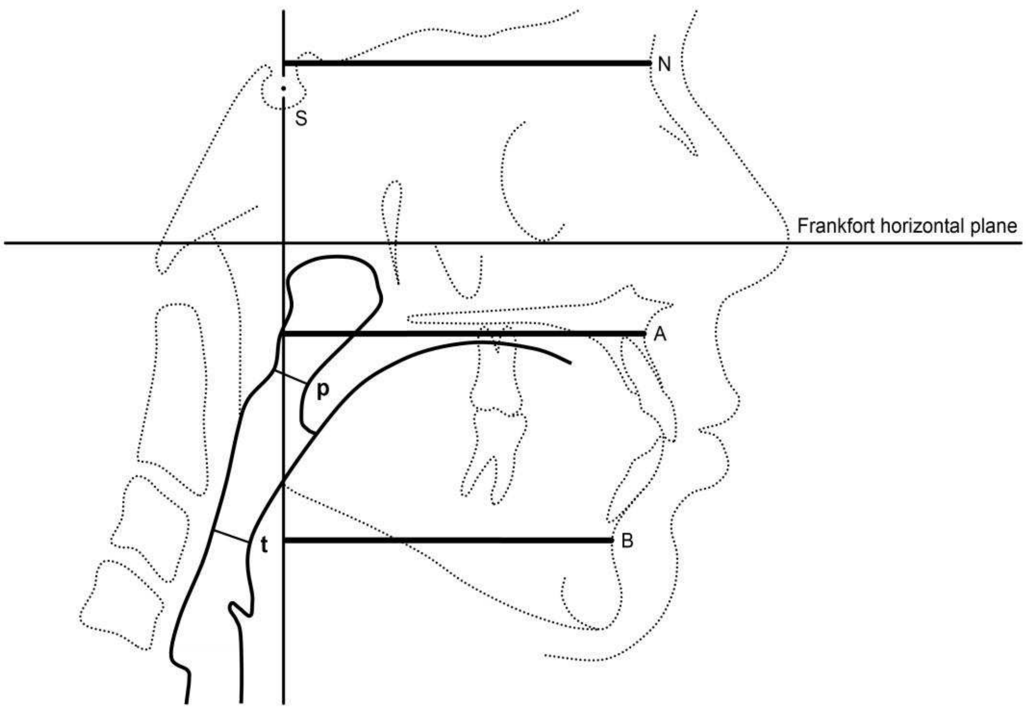


Figure 1B*. Cephalometric distances introduced: Distance to N, A and B. All distances are measured to a line through S, perpendicular to the Frankfort horizontal plane.*



Statistical methods

The data were recorded in Excel (Microsoft Excel for Mac, version 14.0.2, Redmond, Washington, U.S.A.) and analysed with SPSS (IBM SPSS version 20, Armonk, New York, U.S.A.). To determine intra- and interobserver reliability, the intraclass correlation coefficient (ICC) for absolute agreement based on a one-way random effects analysis of variance (ANOVA) was calculated. Descriptive statistics including mean value, median, standard deviation, interquartile range, minimum and maximum were computed for all variables of interest for each age group separately.

The association between age and distances "p" and "t" were investigated graphically and a non-parametric estimate of the mean influence was provided by the Loess-smoother. The one-way ANOVA together with the Sheffe post-hoc-test was applied to disclose the differences in mean values of the distances "p" or "t between different age groups.

The influence of gender on distances "p" and "t" was analysed by a Mann-Whitney-U-test for each age group separately.

The Spearman correlation was computed in order to investigate associations between distances "p" and "t" and cephalometric parameters. Variables that showed tendencies for associations with distances "p" and "t" ($p<0.1$) were chosen for multiple regression model investigations. Backward search procedure was applied in order to obtain the most parsimonious model. The resulting optimal multiple linear regression model was refitted again using the entire procedure. The estimates of the adjusted regression coefficient and the corresponding p-values were provided. The relevance of the model was discussed according to the adjusted R^2-statistic.

Results of statistical analysis with p-value smaller than 0.05 were considered to be statistically significant.

4. Results

Repeatability

The ICC revealed a very good repeatability for all cephalometric measurements. The mean value for all measurements was 0.948 (1. SD 0.142) for intraobserver repeatability and 0.933 (1. SD 0.141) for interobserver repeatability, respectively, as shown in Table 2.

Table 2 *Intraclass correlation coefficient (ICC) for intraobserver and interobserver repeatability.*

	Mean	1. SD	Min.	Max.
Intraobserver	0.948	0.142	0.729	0.995
Interobserver	0.933	0.141	0.700	0.996

Descriptive Analysis

The distributions of airway distances “t” and “p” corresponding to the age (6 to 17 years) of the subjects (n= 880) are shown graphically in Figure 2 and Figure 3, respectively. The mean distances and standard deviation (*SD*) for distance “t” and “p” are presented in Tables 3A and 3B for each age group and gender separately.

Figure 2. *Graphical distribution of airway distance „p“ (shortest airway distance between the soft palate and the posterior pharyngeal wall) corresponding to the age of the subjects (n=880) and Loess interpolation line. Note: lateral cephalograms were almost always taken near the birthday of a subject.*

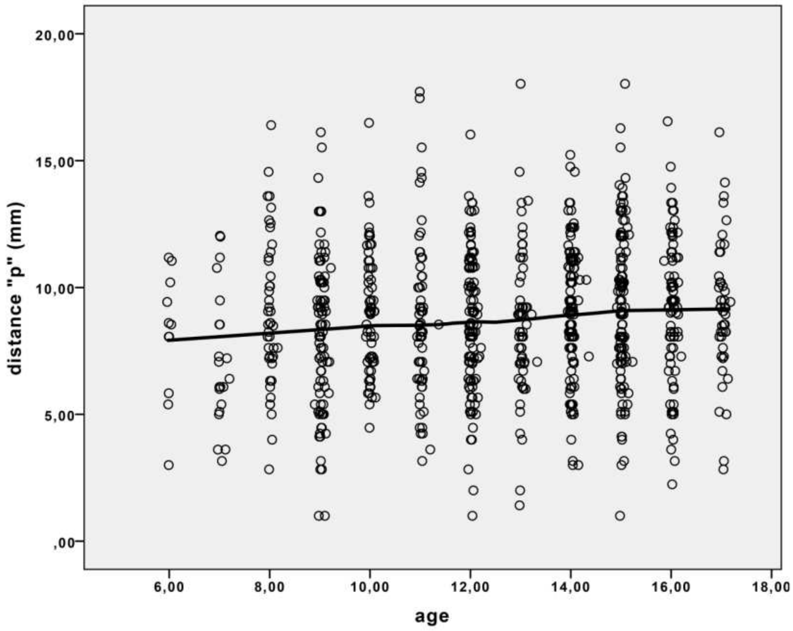


Figure 3. *Graphical distribution of airway distance „t“ (shortest airway distance between the tongue and the posterior pharyngeal wall) corresponding to the age of the subjects (n=880) and Loess interpolation line. Note: lateral cephalograms were almost always taken near the birthday of a subject.*

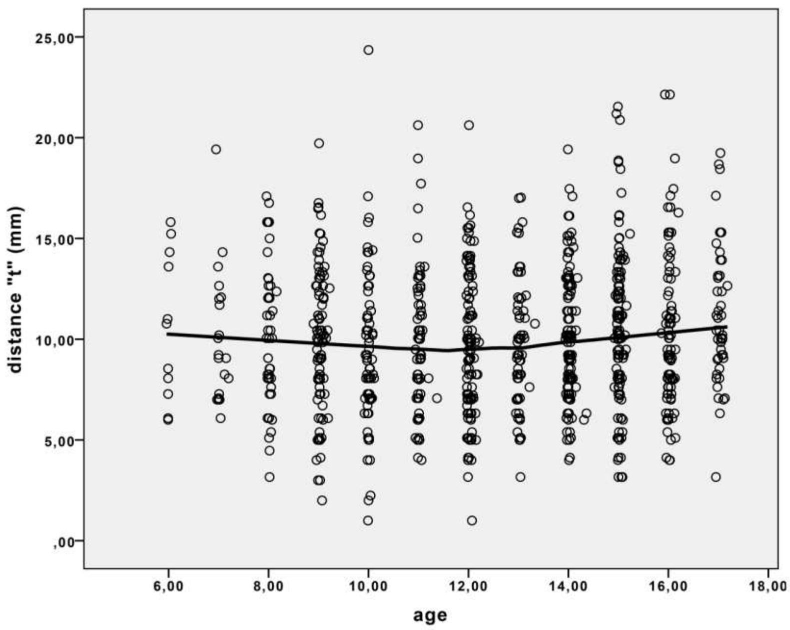


Table 3A *Gender distribution and mean values with standard deviation (SD) for airway distance „p" according to age and gender (n=880 in total). n denotes the amount of subjects in every age group.*

Age group	*n*	Female	Male	Mean distance „*p*" ± 1.SD [mm]		
				Overall	Female	Male
6	11	5	6	8.12 ± 2.52	7.68 ± 2.25	8.49 ± 2.87
7	21	7	14	7.17 ± 2.69	6.52 ± 2.35	7.50 ± 2.87
8	45	23	22	8.94 ± 2.94	9.23 ± 3.28	8.63 ± 2.58
9	93	49	44	8.11 ± 2.98	8.79 ± 3.21	7.15 ± 2.41
10	70	34	36	8.95 ± 2.30	8.91 ± 2.23	9.00 ± 2.39
11	70	38	32	8.75 ± 3.08	8.78 ± 3.41	8.52 ± 2.88
12	111	49	62	8.59 ± 2.66	8.70 ± 2.99	8.49 ± 2.39
13	65	38	27	8.58 ± 2.81	8.72 ± 2.50	8.41 ± 3.28
14	122	64	58	9.02 ± 2.44	8.85 ± 2.49	9.31 ± 2.40
15	134	60	74	9.15 ± 2.86	9.03 ± 2.93	9.25 ± 2.82
16	91	36	55	9.07 ± 2.77	9.30 ± 2.43	9.93 ± 2.99
17	47	19	28	9.15 ± 2.61	10.15 ± 2.88	8.42 ± 2.17

Table 3B *Gender distribution and mean values with standard deviation (SD) for airway distances „t" according to age and gender (n=880 in total). n denotes the amount of subjects in every age group.*

Age group	*n*	Female	Male	Mean distance „*t*" ± 1.SD [mm]		
				Overall	Female	Male
6	11	5	6	10.61 ± 3.67	10.64 ± 3.94	10.58 ± 3.82
7	21	7	14	10.05 ± 3.21	9.97 ± 2.92	10.10 ± 2.87
8	45	23	22	10.17 ± 3.44	9.54 ± 3.53	10.83 ± 3.29
9	93	49	44	10.02 ± 3.49	10.87 ± 3.10	9.08 ± 3.69
10	70	34	36	9.31 ± 3.86	9.58 ± 3.02	9.06 ± 4.55
11	70	38	32	9.98 ± 3.39	10.31 ± 3.78	9.58 ± 2.85
12	111	49	62	9.54 ± 3.54	9.82 ± 3.57	9.33 ± 3.53
13	65	38	27	9.51 ± 3.26	9.25 ± 3.01	9.84 ± 3.65
14	122	64	58	10.02 ± 3.04	10.16 ± 3.32	9.88 ± 2.76
15	134	60	74	10.58 ± 3.61	10.14 ± 3.75	10.94 ± 3.48
16	91	36	55	10.34 ± 3.79	10.30 ± 3.75	10.36 ± 3.85
17	47	19	28	11.19 ± 3.42	12.10 ± 4.00	12.57 ± 2.88

Influence of age on distances “t” and “p”

The one-way ANOVA revealed a statistically significant influence of age on distance ″p“ (p=0.046), but no impact on distance “t“ (p=0.138). This association with “p” can also be seen when comparing Figure 2 and Figure 3: Figure 2 demonstrates the distribution of airway distance “p“ corresponding to the age of the subject (n= 880). The Loess interpolation line shows a slight, but continuous increase of the airway distance „p“ between 6 and 17 years of age. The increase is about 1.03 mm over the 11-year period. Figure 3 shows the distribution of airway distance „t“ in relation to the age of the subject (n=880). The Loess interpolation line demonstrates that the airway distance “t“ decreases slightly between 6 and 12 years of age, and then increases again up to 17 years of age.

Caution should be applied when interpreting the small yet statistically significant age-related increase, as a large interindividual distribution, which can be observed similarly for both airway measurements, is very apparent.

Influence of gender on distances “t” and “p”

The investigation on the association of gender and the distances “t” and “p” found no important influence. Only in the 9-years-age-group significant differences between the genders for airway distances “t” (p-value 0.009) and “p” (p-value 0.002) were found. The statistical results are given in Tables 4A and 4B for distances “p” and “t”, respectively.

Table 4A *Descriptive analysis (mean, median, interquartile range "IQR", minimum "Min", maximum "Max") for „p" at all ages (n=880 in total). P-value of Mann-Whitney-U-test is given to demonstrate significant differences between genders.*

	Female distance "p"				Male distance "p"				Significance
Age group	Mean [mm]	Median [mm]	IQR [mm]	Min ; Max [mm]	Mean [mm]	Median [mm]	IQR [mm]	Min ; Max [mm]	*p-value*
6	7.68	8.06	3.95	5.39 ; 11.05	8.49	9.02	3.29	3.00 ; 11.18	***0.329***
7	6.52	6.08	2.11	3.61 ; 11.18	7.49	7.18	4.52	3.16 ; 12.04	***0.535***
8	9.23	8.60	4.70	4.00 ; 16.40	8.62	8.52	3.29	2.83 ; 13.15	***0.776***
9	8.97	9.06	4.05	1.00 ; 16.12	7.15	7.24	4.20	2.83 ; 11.70	***0.002****
10	8.91	9.06	3.67	5.66 ; 13.60	9.00	9.03	2.97	4.47 ; 16.49	***0.953***
11	8.78	8.40	3.63	3.16 ; 17.72	8.52	8.37	4.32	2.10 ; 14.32	***0.944***
12	8.70	8.54	4.60	1.00 ; 16.03	8.49	8.25	3.35	2.83 ; 13.60	***0.719***
13	8.72	8.94	3.57	1.41 ; 14.56	8.41	8.06	2.22	2.00 ; 18.03	***0.418***
14	8.85	9.00	3.37	3.00 ; 14.76	9.31	9.14	2.99	3.16 ; 15.23	***0.232***
15	9.03	8.74	3.62	1.00 ; 18.03	9.25	9.06	3.90	3.00 ; 16.28	***0.562***
16	9.30	9.50	2.93	4.24 ; 14.76	8.92	9.22	4.40	2.24 ; 16.55	***0.518***
17	9.90	9.75	3.55	3.16 ; 16.12	8.70	8.74	2.52	2.83 ; 13.60	***0.078***

* Correlation is significant at the 0.05 level

Table 4B *Descriptive analysis (mean, median, interquartile range "IQR", minimum "Min", maximum "Max") for „t" at all ages (n=880 in total). P-value of Mann-Whitney-U-test is given to demonstrate significant differences between genders.*

	Female distance "t"				Male distance "t"				Significance
Age group	Mean [mm]	Median [mm]	IQR [mm]	Min ; Max [mm]	Mean [mm]	Median [mm]	IQR [mm]	Min ; Max [mm]	*p-value*
6	10.64	11.00	7.73	6.08 ; 15.23	10.58	9.66	7.15	6.00 ; 15.81	***1.000***
7	9.97	9.06	5.65	7.00 ; 14.32	10.09	9.63	4.79	6.08 ; 19.42	***0.913***
8	9.54	8.54	4.46	3.16 ; 17.09	10.83	11.29	4.95	4.47 ; 16.76	***0.195***
9	10.87	10.44	4.09	4.00 ; 16.55	9.08	8.77	5.19	2.00 ; 19.72	***0.009****
10	9.58	9.08	4.71	4.00 ; 15.81	9.06	9.77	4.58	1.00 ; 24.35	***0.350***
11	10.31	10.13	5.18	4.00 ; 20.62	9.58	9.61	4.04	4.12 ; 15.03	***0.604***
12	9.82	9.85	5.73	1.00 ; 16.16	9.33	9.06	4.50	3.16 ; 20.62	***0.354***
13	9.25	9.22	4.89	3.16 ; 15.52	9.84	9.06	6.27	5.00 ; 17.03	***0.786***
14	10.16	9.22	4.59	4.00 ; 19.42	9.88	9.85	4.67	5.00 ; 16.12	***0.689***
15	10.14	9.75	4.67	3.16 ; 21.54	10.94	10.75	3.68	3.16 ; 21.19	***0.167***
16	10.29	9.22	5.65	4.00 ; 18.97	10.36	10.05	3.66	4.00 ; 22.14	***0.929***
17	11.59	11.78	5.09	3.16 ; 19.24	10.41	9.93	4.37	2.24 ; 18.68	***0.170***

* Correlation is significant at the 0.05 level

Correlation analysis to other cephalometric parameters

The Spearman correlation analysis (2-tailed) revealed several statistically significant correlations between the distances "t" and "p" to clinical parameters. These are presented in Table 5.

Table 5 *Spearman Correlation analysis for distance „t" and distance „p".*

	Distance „t"		Distance „p"	
	Correlation coefficient	*p-value*	Correlation coefficient	*p-value*
Ratio A/N	0.111	*0.001*	0.082	*-0.016*
Ratio B/N	0.126	*0.000***	0.118	*0.000***
Ratio A+B/N	0.129	*0.000***	0.114	*0.001***
SNA	0.112	*0.001***	0.084	*0.012**
SNB	0.115	*0.001***	0.110	*0.001***
ANB	-0.120	*0.727*	-0.027	*0.419*
WITS	-0.007	*0.844*	-0.027	*0.422*
SpaSpp/MGo	-0.017	*0.619*	-0.077	*0.032**
NS/MGo	-0.410	*0.221*	-0.064	*0.057*
MGo/Ar	0.010	*0.759*	-0.040	*0.232*
Overjet	-0.058	*0.086*	-0.037	*0.278*
Overbite	-0.055	*0.102*	-0.026	*0.441*
NS/Gn	-0.098	*0.004***	-0.089	*0.008***

* Correlation is significant at the 0.05 level (2-tailed)
** Correlation is significant at the 0.01 level (2-tailed)

Significant positive correlations for distance "t" were found with the cephalometric values of ratio B/N , ratio A+B/N, SNA, SNB and a significant negative correlation with NS/Gn. All significant correlation had, however, small correlation coefficients.

For distance "p" positive correlations were found with ratio B/N, ratio A+B/N, SNA, SNB and negative correlations with NS/Gn and SpaSpp/MGo; all correlations for distance "p" had also a low correlation coefficient.

No correlations to ANB were found, neither for distance "t", nor for distance "p".

Variables that showed statistical tendencies ($p < 0.1$) or associations with distance "p" and distance "t" were chosen for multiple regression model investigations. These are presented in Table 6A for distance "t" and Table 6B for distance "p".

Table 6A *Multiple linear regressions on 880 observations for explanation of distance „t". Possible variables were: Go-Pg, WITS, MGo/Ar, overbite, „ratio B/N".*

	distance „t"		
	coefficient	SE	*p-value*
Go-Pg	0.100	0.024	*0.000***
WITS	0.099	0.047	*0.037**
MGo/Ar	0.069	0.025	*0.006***
Overbite	-0.133	0.061	*0.029**
Ratio B/N	4.301	1.898	*0.024**

Table 6B *Multiple linear regressions on 880 observations for explanation of distance „p". Possible variables were: Go-Pg, SNB, SpaSpp/MGo, SN/Mgo.*

	distance „p"		
	coefficient	SE	*p-value*
Go-Pg	0.031	0.018	*0.820*
SNB	0.102	0.038	*0.007***
SpaSpp/MGo	-0.730	0.034	*0.031**
SN/MGo	-0.084	0.039	*0.031**

Multiple linear regressions were carried out on 880 observations for interpretation of distances "t" and "p". Possible variables for distance „t" were: Go-Pg, WITS, MGo/Ar, overbite and „ratio B/N".

Possible variables for distance „p" were: Go-Pg, SNB, SpaSpp/MGo, SN/MGo.

The adjusted Coefficient of determination (R^2) of the multiple linear regressions-model was 0.18 for distance “p” and 0.31 for distance ”t”, indicating the inherent insufficiency of the model to adequately predict “p” or “t”.

5. Discussion

Rationale behind this study and the parameters used

This study investigated the pharyngeal airway dimensions based on 880 lateral cephalometric radiographs from healthy, orthodontically untreated children aged 6 to 17 years. It is the first attempt to establish reference values of airway dimensions based on a large growth study.

Although several notable craniofacial studies exist (Riolo ML, 1974; Prahl-Andersen B, 1979; Bishara, 1981; Roche, 1992; Bhatia SN, 1993; Hunter *et al.*, 1993; el-Batouti *et al.*, 1994), the Zurich craniofacial Growth study was used owing to its uniqueness in two ways. First, it enables to derive a large sample size of untreated subjects of the same cohort without pooling. This stands in contrast to previous studies which used sometimes far smaller sample sizes or occasionally even the data of treated subjects (Lee *et al.*, 1987). The abundance of material is not just a nice feature. It permits the division of the data in subgroups by gender and age, while leaving every subgroup with enough statistical power.

Second, the Zurich craniofacial Growth study is matchless because it is the sole growth study in which the data collection was performed always very close to the subject's birthday. The implication of this fact is that no thresholding is necessary when dividing the sample in different age groups.

A number of limitations of lateral cephalometry have been discussed (Lowe *et al.*, 1986; Battagel and L'Estrange, 1996; Finkelstein *et al.*, 2001), particularly the inadequate representation of three-dimensional upper airway structure with a two-dimensional radiograph. Obviously, information is lost concerning the transverse dimension of the airway, and its value as a diagnostic tool has been questioned, as a true assessment of airway dimensions would require a three-dimensional recording technique such as computerized tomography (CT) or magnetic resonance imaging (MRI) (Lowe *et al.*, 1986; Rodenstein *et al.*, 1990).

Due to the fact that the upper airway is not a rigid, but a dynamic structure, measurements are also influenced by other factors. These include supine or upright positioning, awake or asleep muscle tone, inspiration or expiration, duration of x-ray exposure and mouth opening. For example, since both the soft palate and tongue are large soft tissues without rigid bony support, the genioglossus muscle is considered to be a key muscle in maintaining a patent upper airway. Therefore the airway dimensions on the radiographs are also determined by the activity of this muscle and it is for this reason that the airway dimensions will be influenced by breathing or swallowing as well.

Considering these circumstances, it becomes evident that even a three-dimensional radiographic representation does not account for the true clinical circumstances under which OSA may occur. Also the simple calculation of an airway volume is a poor indicator of airway patency as, for example, length increases the volume of a tube (suggesting lower resistance) when in reality it increases the resistance of a tube (Poisseuilles law). For clinical relevance, it is therefore primordial that the smallest cross-sectional area (Ogawa *et al.*, 2007) (CSA) has to be calculated. The study carried out by Ogawa and co-workers found significant differences in the smallest cross-section areas between patients with OSA and those without. Further, the Ogawa study shows that the anterior-posterior dimension is the most decisive dimension of the minimum cross-section segment, because it shows significant group differences between OSA und non-OSA patients in this area (OSA: 4.6mm / non-OSA: 7.8mm). The differences in transverse dimension, on the other hand, were also present but not significant. Based on the findings of the Ogawa study it is safe to presume that although an airway assessment based on lateral cephalograms will be limited on a two-dimensional reflection of the airway, it nevertheless will represent the critical and pivotal distances for airway patency.

The conventional lateral cephalogram remains therefore not only a solid and routine diagnostic tool for orthodontics, but also a legitimate instrument for airway measurements. Measurements based on lateral radiographs have been used previously in several airway studies (de Freitas *et al.*, 2006; Ogawa *et al.*, 2007; Aboudara *et al.*, 2009; Pirila-Parkkinen *et al.*, 2011; Alves *et al.*, 2012). In particular, cephalogram-based studies confirmed a correlation between the measured dimensions and the clinical condition in OSA and snoring subjects (Finkelstein *et al.*, 2001), validating the assumption that sleep-disordered breathing is associated with statistically significant changes in a number of cephalometric measurements. Moreover, it was established that effects accorded to orthodontic therapy such as Activator-Headgear-treatment have the potential to increase pharyngeal dimensions (Hanggi *et al.*, 2008).

The implication that lateral cephalometric radiograph, a conventional orthodontic method used for determining craniofacial morphology and possible airway obstruction, can also be used as an airway-screening tool (Aboudara *et al.*, 2009), is, of course, that there is no clinical need for more rigorous investigations with potentially higher radiation doses, such as three-dimensional recording techniques.

This line of thinking was recently substantiated by a study that indicated the lateral cephalogram to be a valid imaging method and a good screening tool for measuring dimensions of the nasopharyngeal and retropalatal region in children (Pirila-Parkkinen *et al.*, 2011). In this study, a significant correlation between nasopharyngeal and retropalatal cephalometric variables and MRI findings could be demonstrated, and again, both techniques revealed the narrowest measurement to be the anterior-posterior distance located in the retropalatal region.

Distances “t” and “p”

In this present study the shortest airway distances were used to evaluate the airway as described in other airway studies (McNamara, 1984; Rodenstein *et al.*, 1990; Finkelstein *et al.*, 2001; Pirila-Parkkinen *et al.*, 2011; Alves *et al.*, 2012). The minimal distances were evaluated because of their clinical relevance in OSA patients and because they can be easily and reliably measured.

The measurement results of distance “p” and “t” show high interindividual variations, but only small differences between the different age groups. The individual variation of the parameters measured is substantial enough to render the use of mean values, when applied to individual cases, as exceedingly questionable.

Influence of age on distances “t” and “p”

The findings in this study illustrate for distance “t” that the airway distance decreases very slightly between 6 and 12 years of age, and then increases slightly up to 17 years of age. The results for distance “t“ are in agreement with an earlier study (McNamara, 1984), which found no noticeable changes with age and showed the average value of this measurement to be between 10 and 12 mm (9 – 11 mm without magnification).

Similar results were also found in other airway studies (Ogawa *et al.*, 2007; Hanggi *et al.*, 2008; Alves *et al.*, 2012).

Distance "p" displayed a slight continuous increase between 6 and 17 years of age. The increase is about 1.03 mm over this 11-year period. These findings for distance "p" also confirm the results from McNamara (1984) that this dimension increases with age in adolescence. Possibly, distance "p" is also influenced by a decline in adenoid size during this growth period.

Influence of gender on distances "t" and "p"

Sexual dimorphism in craniofacial dimensions is a fact that has been established in various analyses (Schudy, 1965; Bishara and Jakobsen, 1985; Siriwat and Jarabak, 1985; Nanda, 1988).

Yet, maybe surprisingly, there were no differences in airway dimensions of distance "t" and "p" between male and female subjects.

In general, females are smaller in stature than men (having less muscle mass and smaller heads) and subsequently require less oxygen. If airways in women are of similar dimensions to those in men, it follows that their airways must be larger in relative terms and this may be one of the reasons that women would be less prone to OSA than men. Further studies are, however, needed to substantiate this hypothesis.

Correlation to other cephalometric parameters

Only few and weak correlations of distance "p" and "t" to the cephalometric landmarks were found. In fact, no correlation was found to otherwise important variables such as the angle of the mandible or skeletal class (neither according to the ANB angle nor the WITS appraisal). A significant, however weak, correlation could be established to the pro- and retrognathism of the maxilla and mandible to the Y-axis.

Regression-models for distance “p” and “t” were created with the correlating factors and the adjusted coefficient of determination (R^2) was calculated. The coefficient of determination is used in the context of statistical models. Its main purpose is the prediction of future outcomes on the basis of other related information. R^2 is a number used to describe how well a regression line fits a set of data. The evaluated R^2 for the regression-models for distance “p” and “t” respectively indicates that the established model will not fit any future data very well. This corroborates the concerns raised above on the correlations, which entailed low correlation coefficients and renders the association between airway dimensions and other craniofacial measurements as quite weak.

Ramifications of the findings of this study

Considering how abundant craniofacial growth and development is during the growth period between 6 to 17 years of age, it is contrary to expectation that no radical change in the upper airway dimensions were found in this study. A possible implication of these minimal changes in airway dimensions over these 11 years would be the importance of an early minimal airway diameter to enable the airway patency for respiration in later years. It seems that the upper airway dimensions are formed and matured in the early periods of growth, and those years seem to be of high relevance to ensure the later physiological need of an adequate airflow.

As shown in recent research, airway dimensions can be influenced by functional appliances (Hanggi *et al.*, 2008). In light of the findings of this present study demonstrating stable and unaltered airway dimensions throughout the entire growth, orthodontic therapy could have a welcome additional effect to increase these otherwise unchanging airway dimensions. There is scientific evidence that with regard to adults, the dimensions seem to steadily decrease with progressing age due to physiological changes, including weight gain, based on the loss of tissue elasticity (Martin *et al.*, 1997). Hence, it could be rationalized that functional appliances might have a preventive effect in regard to OSA in retrognathic, yet asymptomatic orthodontic patients.

There are some limitations to this study. To gain more information about the airway dimensions and their physiological changes in growing children, true longitudinal studies of untreated subjects would be needed, but for ethical reasons this is difficult. Within the limitations of this study, the results suggest that upper airway dimensions in growing children from 6 to 17 years of age remain remarkably stable on average but with very large interindividual variations and contrary to other studies (Abu Allhaija and Al-Khateeb, 2005; Alves *et al.*, 2012) they are quite independent of skeletal parameters.

6. Conclusion

The airway distances “p” and “t” show high interindividual variations and render the use of a mean value as reference on individuals questionable. Small differences between the different age groups could be observed, but no differences between the genders. Only weak correlations of distances “p” and “t” to certain cephalometric landmarks were found, but no correlation with ANB. The results show that upper airway dimensions in growing children from 6 to 17 years of age remain remarkably stable on average and suggest that the airway dimensions are being established in early childhood.

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8. Legal approval of the Federal Commission of Experts for Professional Secrecy in Medical Research

Sonderbewilligung
zur Offenbarung des Berufsgeheimnisses zu Forschungszwecken
im Bereich der Medizin und des Gesundheitswesens

Die Expertenkommission für das Berufsgeheimnis in der medizinischen Forschung,
hat im Zirkularverfahren vom 25. Juli 2011,
gestützt auf Artikel 321bis des Strafgesetzbuches (StGB; SR *311.0*);
Artikel 1, 2, 9, 10, 11 und 13 der Verordnung vom 14. Juni 1993 über die Offenbarung des Berufsgeheimnisses im Bereich der medizinischen Forschung (VOBG; SR *235.154*);
in Sachen *Zentrum für Zahnmedizin, Universität Zürich, Projekt «Zürcher kraniale Wachstumsstudie – eine retrospektive Analyse von Röntgenbildern unbehandelter Kinder»*, betreffend Gesuch vom 16. Juni 2011 für eine Sonderbewilligung zur Offenbarung des Berufsgeheimnisses im Sinne von Artikel 321bis StGB zu Forschungszwecken im Bereich der Medizin und des Gesundheitswesens,
verfügt:

1. Bewilligungsnehmer

a) Dr. med. dent. Raphael Patcas, Oberassistent an der Klinik für Kieferorthopädie und Kinderzahnmedizin des Zentrums für Zahnmedizin der Universität Zürich, wird als verantwortlichem Projektleiter unter nachfolgenden Bedingungen und Auflagen eine Sonderbewilligung gemäss Artikel 321bis StGB sowie Artikel 2 VOBG zur Entgegennahme nicht anonymisierter Daten im Rahmen von Ziffer 2 und 3 erteilt.

b) Dr. med. dent. Luca Signorelli, externer Mitarbeiter der Klinik für Kieferorthopädie und Kinderzahnmedizin des Zentrums für Zahnmedizin der Universität Zürich, und Dr. med. dent. Michael Hänggi, Oberassistent an der Klinik für Kieferorthopädie und Kinderzahnmedizin des Zentrums für Zahnmedizin der Universität Zürich, wird unter nachfolgenden Bedingungen und Auflagen eine Sonderbewilligung gemäss Artikel 321bis StGB sowie Artikel 2 VOBG zur Entgegennahme nicht anonymisierter Daten im Rahmen von Ziffer 2 und 3 erteilt.

Die Bewilligungsnehmer haben eine Erklärung über die ihnen gemäss Artikel 321bis StGB auferlegte Schweigepflicht zu unterzeichnen und der Expertenkommission zuzustellen.

2. Umfang der Sonderbewilligung

a) Der Ärzteschaft der Klinik für Kieferorthopädie und Kinderzahnmedizin des Zentrums für Zahnmedizin der Universität Zürich sowie deren Hilfspersonen wird die Bewilligung erteilt, den Bewilligungsnehmern gemäss Ziffer 1 Zugang zu den Daten und Röntgenbildern (Handröntgen und seitliches Fernröntgenbild) zu gewähren, die in der Zeit von 1981–1984 im Rahmen eines damals durchgeführten Projektes von insgesamt 884 Zürcher Schulkindern erhoben bzw. angefertigt wurden. Die Datenbekanntgaben dürfen einzig dem in Ziffer 3 umschriebenen Zweck dienen.

b) Mit der Bewilligungserteilung entsteht für niemanden die Pflicht zur Datenbekanntgabe.

3. Zweck der Datenbekanntgabe

Die gestützt auf die vorliegende Bewilligung bekannt gegebenen Personendaten, die dem medizinischen Berufsgeheimnis gemäss Artikel 321 StGB unterstehen, dürfen nur für das Projekt «Zürcher kraniale Wachstumsstudie – eine retrospektive Analyse von Röntgenbildern unbehandelter Kinder» verwendet werden.

4. Schutz der bekannt gegebenen Daten

Die Bewilligungsnehmer haben die nach den datenschutzrechtlichen Bestimmungen erforderlichen technischen und organisatorischen Massnahmen zu treffen, um die Daten vor unbefugtem Zugriff zu schützen.

5. Verantwortlichkeit für den Schutz der bekannt gegebenen Daten

Die Verantwortung für den Schutz der bekannt gegebenen Daten trägt der verantwortliche Projektleiter, Dr. med. dent. Raphael Patcas.

6. Auflagen

a) Die für das Projekt benötigten Daten sind so bald als möglich zu anonymisieren.

b) Unberechtigten Personen darf kein Einblick in nicht anonymisierte Daten gewährt werden.

c) Die Massnahmen gemäss Ziffer 4 haben dem Stand der Technik zu entsprechen.

d) Nicht anonymisierte Daten sind zu vernichten, sobald sie nicht mehr benötigt werden.

e) Projektergebnisse dürfen nur in vollständig anonymisierter Form veröffentlicht werden, d.h. es dürfen keinerlei Rückschlüsse auf die betroffenen Personen möglich sein. Nach Abschluss des Projektes ist der Expertenkommission ein Exemplar allfälliger Publikationen zur Kenntnisnahme zuzustellen.

f) Die Bewilligungsnehmer haben die zuständige Ärzteschaft der Klinik für Kieferorthopädie und Kinderzahnmedizin des Zentrums für Zahnmedizin der Universität Zürich über den Umfang der erteilten Bewilligung schriftlich zu informieren. Das Schreiben ist vor dem Versand dem Sekretariat der Expertenkommission zu Handen des Präsidenten zur Kenntnisnahme zuzustellen.

7. Rechtsmittelbelehrung

Gegen diese Verfügung kann gemäss Artikel 44 ff. des Bundesgesetzes vom 20. Dezember 1968 über das Verwaltungsverfahren (VwVG; SR *172.021*) innert 30 Tagen seit deren Eröffnung bzw. Publikation beim Bundesverwaltungsgericht, Postfach, 3000 Bern 14, Beschwerde erhoben werden. Die Beschwerde ist im Doppel einzureichen und hat die Begehren, deren Begründung mit Angabe der Beweismittel und die Unterschrift der beschwerdeführenden Partei oder ihres Vertreters oder ihrer Vertreterin zu enthalten. Die angefochtene Verfügung und die als Beweismittel angerufenen Urkunden sind beizulegen.

8. Mitteilung und Publikation

Diese Verfügung wird den Bewilligungsnehmern und dem Eidgenössischen Datenschutz- und Öffentlichkeitsbeauftragten schriftlich mitgeteilt. Das Verfügungsdispositiv wird im Bundesblatt veröffentlicht. Wer zur Beschwerde legitimiert ist, kann innert der Beschwerdefrist beim Sekretariat der Expertenkommission, Bundesamt für Gesundheit, Abteilung Recht, 3003 Bern, nach telefonischer Voranmeldung (031 322 94 94) Einsicht in die vollständige Verfügung nehmen.

18. Oktober 2011

Expertenkommission für das Berufsgeheimnis in der medizinischen Forschung

Der Vizepräsident: Rudolf Bruppacher